Francesconi, M., Minichino, A., Khandaker, G. M., Midouhas, E., Lewis, G., & Flouri, E. (2020). Internalising symptoms mediate the longitudinal association between childhood inflammation and psychotic-like experiences in adulthood. *Schizophrenia Research*, *215 (2020)*, 424-429. https://doi.org/10.1016/j.schres.2019.07.035

Internalising symptoms mediate the longitudinal association between childhood inflammation and psychotic-like experiences in adulthood.

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Abstract: 208

Main text: 2890

Abstract

Psychotic-like experiences (PLEs) are part of a continuum of psychosis. Previous longitudinal studies highlighted a relationship between peripheral inflammation during childhood and onset of PLEs in adulthood. In this study, we tested if this association is mediated by internalising and externalising symptoms experienced during childhood and adolescence. To test this hypothesis, we used data from the Avon Longitudinal Study of Parents and Children (ALSPAC). We investigated a subsample of 4,525 individuals from this cohort with data on interleukin 6 (IL-6) and C-reactive protein (CRP) in childhood (age 9 years). We measured PLEs at age 18 years, and we used latent growth curve modelling to estimate longitudinal trajectories of internalising and externalising symptoms from ages 9 to 16 years. The individual predicted values of the intercept (set at baseline, 9 years) and the slope (rate of annual change) were then used in the mediation analysis. There was evidence for full mediation by the intercept of internalising symptoms. Our findings suggest that inflammation during childhood may be relevant for the future onset of PLEs via its association with a high level of internalising symptoms. These findings, although obtained from a non-clinical population, provide an additional step in advancing knowledge on the relationship between inflammation and symptoms of the psychosis continuum.

Keywords: ALSPAC, externalising, inflammation, internalising, psychotic-like experiences

1. Introduction

Psychotic-like experiences (PLEs) are subclinical, attenuated, psychotic symptoms considered to represent the healthier end of the psychosis continuum (Unterrassner et al., 2017, Nelson et al., 2012), but still associated with a range of common psychiatric disorders, such as major depressive disorder or anxiety disorders (van Os and Reininghaus 2016). PLEs are typically considered benign, given their transitory nature and their relatively high prevalence in the general population (~7%) (Linscott and Van Os 2013). However, a non-negligible proportion (~20%) become persistent and in some cases (~7%) predate the onset of a full-blown psychotic disorder (Linscott and Van Os 2013). Their often-benign nature notwithstanding, PLEs and psychotic disorders share etiological risk factors, demographic characteristics and cognitive correlates (Ermel et al., 2018, Orr et al., 2014). Thus, PLEs measured in the general population represent a unique opportunity to gain insight on the psychosis continuum.

Psychotic disorders are highly debilitating and impose a severe burden on sufferers, their families and the wider society (Millan et al., 2016). This burden is greatly increased by the frequent co-occurrence of chronic physical health conditions, such as obesity, diabetes and cardiovascular disease (Cadenhead et al., 2018, Correll et al., 2014), which underlie the 10 to 20 years' drop in life-expectancy observed in sufferers (Lawrence et al., 2013). In line with the hypothesis of a psychosis continuum, an increased risk of physical comorbidities has also been shown in individuals with PLEs (Moreno et al., 2013). The high comorbid rates of physical conditions and psychotic disorders/PLEs have led to the hypothesis of a shared pathophysiological background (Minichino et al., 2017), which, in turn, has attracted interest in the role of inflammation and the immune system.

The hypothesized role of the immune system as the connecting dot between physical and mental health is, after the last two decades of research, receiving increasing levels of support. With respect to psychotic disorders, several immune loci achieved genome wide significance in their association with psychotic disorders (Ripke et al., 2014) and meta-analytic evidence showed increased levels of pro-inflammatory cytokines, such as interleukin 6 (IL-6), in sufferers compared to healthy controls (Pillinger et al., 2018, Miller et al., 2011, Upthegrove et al., 2014). Taken together, these findings led some to hypothesize a causal role for inflammation in psychosis (Al-Diwani et al., 2017).

A test of this hypothesis has been provided by longitudinal general-population studies that have established long-term links between inflammation in childhood and PLEs in young adulthood (Downs et al., 2013, Khandaker et al., 2014). A previous Mendelian randomization study from the ALSPAC cohort has also reported association between genetic variants regulating activity of IL-6 and risk of psychosis, suggesting reverse causality or residual confounding are unlikely explanations for previously reported associations between IL-6 and psychosis (Khandaker et al., 2018). Longitudinal general-population studies have also established links between a pro-inflammatory status in otherwise healthy children and increased levels of psychopathology in the form of internalising (i.e., anxiety, depression, or social withdrawal) (Ridout et al., 2014, da Silva et al., 2017, Slopen et al., 2013) and externalising symptoms (i.e., hyperactive, aggressive, antisocial, or oppositional behaviors) (Slopen et al., 2013). Inflammation during childhood has been suggested to result from a number of different sources (Slopen et al., 2015), including a history of psychosocial adversity, early-life infections and autoimmune diseases (Baumeister et al., 2016). In turn, the pro-inflammatory physiologic response to early adversities has recently been suggested to play a role in the onset of internalising and externalising symptoms (Flouri et al., 2019).

Based on these observations, and the now established link between PLEs and both internalizing and externalizing symptoms (Downs et al., 2013, Khandaker et al., 2014), we carried out this study to investigate if internalising and externalising symptoms mediate the association between a pro-inflammatory status in childhood and the onset of PLEs in adulthood. Shedding light on the association between inflammation and PLEs will improve understanding of the pathophysiology of the psychosis continuum. Further, it will provide a background for future studies investigating tailored therapeutic approaches, which are greatly needed especially in the prodromal phase of psychotic spectrum disorders where no effective interventions are currently available (Davies et al., 2018).

2. Materials and methods

2.1 Study design and participants

We used data from the Avon Longitudinal Study of Parents and Children (ALSPAC), a general population birth cohort. ALSPAC is a birth cohort study designed to assess environmental factors during and after pregnancy that might affect the development, health, or wellbeing of the child (Boyd et al., 2013). 14,541 pregnant women living in Bristol, UK, and surrounding areas, were enrolled for the study. (Please note that the study website contains details of all the data that is available through a fully searchable data dictionary and variable search tool: http://www.bristol.ac.uk/alspac/researchers/our-data/.) From the first trimester of pregnancy parents completed postal questionnaires about themselves and the study child's health and development. Children were invited to attend annual assessment clinics, including face-to-face interviews and psychological and physical tests from age 7 years onward.

Additional children were recruited using the original enrolment definition from the participating children's age 7 years onwards, increasing the number to 15,445 pregnancies to date (Fraser et al., 2013). Ethics approval was received from the ALSPAC Law and Ethics Committee and local research ethics committees. All participants provided written informed consent and there was no financial compensation (more details at www.alspac.bris.ac.uk). Our study's analytic sample included 4,525 childrenss (singletons and first-born multiples) who had data on inflammation at age 9 years [measured in ALSPAC with C-reactive protein (CRP) and IL-6] and who did not report an infection at the time of blood collection or during the preceding week.

2.2 Measures

Inflammation, age 9 years

In ALSPAC blood samples were collected from participants during the clinic visit at 9 years. Blood samples were collected from nonfasting participants and were immediately spun and frozen at −80°C. IL-6 (pg/mL) was measured by enzyme-linked immunosorbent assay (R&D Systems) and high-sensitivity CRP (mg/L) was measured by automated particle-enhanced immunoturbidimetric assay (Roche). All inter-assay coefficients of variation were less than 5%. In ALSPAC total sample IL-6 (IL-6 n=5,072) values ranged from 0.007 to 20.051 pg/mL while CRP (CRP n=5,082) values ranged from 0.01 to 67.44 mg/L (60 children had values over 10 mg/L). Both CRP and IL-6 were log-transformed for the analyses presented here.

Internalising and externalising symptoms, ages 9, 11, 13 and 16 years

Internalising and externalising symptoms, following the measurement of inflammation and preceding the measurement of PLEs, were assessed using the mother-rated Strengths and Difficulties Questionnaire (SDQ) at ages 9, 11, 13 and 16 years. The SDQ is a valid and reliable tool for measuring emotional and behavioural difficulties in children (Goodman 2001). It includes 20 items related to children's difficulties (in the past 6 months) scored on a 3-point scale with 0 = 'not true', 1 = 'somewhat true' and 2 = 'certainly true'. Items can be summed to form four scales (emotional symptoms, conduct problems, hyperactivity, and peer problems), or two (internalising problems, the sum of the scores on the emotional and peer problems items, and externalising problems, the sum of the scores on the conduct problems and hyperactivity items) (Goodman et al., 2010). Given their clinical relevance, internalising and externalising symptoms were the focus in our analysis (Fergusson et al., 2005, Reef et al., 2011).

Psychotic-like experiences, age 18 years

Psychotic experiences were assessed through the face-to-face, semi-structured Psychosis-Like Symptom Interview (PLIKSi) (Zammit et al., 2013). The PLIKSi has been used in psychiatric and epidemiological research since 2008 and consists of 12 core questions, 7 derived from the Diagnostic Interview Schedule for Children, Version IV (DISC-IV) (Shaffer et al., 2000) and 5 from the Schedules for Clinical Assessment in Neuropsychiatry (SCAN) (WHO 1994), version 2, and it assesses the presence of delusions (spied on, persecution, thoughts read, reference, control, grandiosity and other unspecified delusions), thought interference (broadcasting, insertion and withdrawal) and hallucinations (visual and auditory). The ALSPAC interviewers were trained psychology graduates and coded according to the definitions and rating rules for the SCAN. After cross-questioning, interviewers rated psychotic experiences as not present, suspected, or definitely psychotic.

For suspected or definite psychotic experiences, interviewers also reported the frequency; impact on affect, impact on social function, impact on educational/occupational function; help seeking from professionals; and attributions, such as fever, hypnopompic/hypnogogic state, or substance use. In our analysis, we defined individuals with psychosis-like symptoms as those with definite psychotic experiences.

Covariates

We adjusted for a number of covariates known to be associated with children's inflammation and internalising and externalising symptoms but also with psychotic-like experiences. These included gender, ethnicity (white, non-white), maternal depression, which in ALSPAC was assessed with the Edinburgh Postnatal Depression Scale (EDPS) (Cox et al., 1987) at 32 weeks of pregnancy, parental socioeconomic status at the same time-point, which we approximated by maternal education (below O-level, O-level only, A-level only, university degree or more) and paternal social class (I, II, III (non-manual), III (manual), IV, V), and obesity status (body mass index (BMI) above the 95th percentile for children of the same age) (Lobstein et al., 2004). BMI (weight (kg)/height $(m)^2$) was measured during the clinic visit at age 9 years. Consistent with previous literature, we decided to use an antenatal maternal depression measurement as it has been found to be strongly associated with subsequent development of mental health problems during childhood and adulthood (Pearson et al., 2013).

2.3 Statistical analysis

All analyses were performed in STATA 15.0 (StataCorp 2017).

We used latent growth curve modelling (LGM) to estimate longitudinal trajectories of internalising and externalising symptoms from ages 9 to 16 years. Internalising and

externalising symptoms were assessed at two-year intervals from 9 to 13 years and three-year intervals from 13 to 16 years. The individual predicted values of the intercept (set at baseline, 9 years) and the slope (rate of annual change) were then used as mediators in the mediation analysis. Using the predict command in STATA we generated predictions for the out-of-sample cases, i.e., the cases that were not used in the original estimation. In this way we were able to estimate the intercept and the slope for internalising and externalising symptoms in our whole analytic sample (n=4,525). Two mediation models (details below) were then fitted using seemingly unrelated regression analysis. In our mediation models, both mediators (internalising and externalising symptoms) and exposures (CRP or IL-6) had complete data. Missingness among the confounders and PLIKSi ranged from 0.08% (gender) to 44.7% (PLIKSi). Missing data were then imputed (20 imputed datasets) using multiple imputation by chained equations. We used internalising symptoms, externalising symptoms, inflammation and covariate data to predict missingness on PLIKSi.

3. Results

3.1 Descriptive analyses

Table 1 shows the descriptive characteristics of our sample, including means and proportions for the exposures, outcome, and covariates. The distribution of males and females was similar in our sample, whereas, as expected given the design of ALSPAC, the majority was white (96%). A high proportion of mothers reported an educational level equal to or above O-level and the majority of our sample was in non-manual social classes (I to III). A 4% of our sample experienced psychosis-like symptoms at 18 years and almost 5% was obese at age 9 years. Correlations between the study variables were low to moderate, as expected (Supplementary Table S1).

3.2 Mediation models

Model 1

In our first model, we tested the direct association between inflammatory markers (IL-6 and CRP) measured at 9 years and the presence of psychosis-like symptoms at age 18 years. As shown in Figure 1, IL-6 was associated with psychotic experiences (β=0.037; $p<0.05$; CI=0.00-0.07), but CRP was not. We therefore decided to drop CRP from all further analyses and focus on IL-6.

Model 2a

In this model, we tested whether the intercept or the slope of internalising symptoms mediated the effect of IL-6 on psychosis-like symptoms. We found that only the intercept of internalising symptoms mediated the association between inflammation and psychotic experiences (Figure 1). The indirect effect was significant (β=0.007; $p<0.01$; CI=0.00-0.01) as was the total effect (β=0.037; $p<0.05$; CI=0.00-0.07), whereas the direct effect of IL-6 on psychotic experiences was attenuated fully. These results suggest complete mediation.

Model 2b

We also explored if the intercept or the slope of externalising symptoms mediated the association between IL-6 and psychosis-like symptoms. We found that neither the intercept nor the slope of externalising symptoms mediated this association.

Model 3

In our final model, we tested if the mediator effect found was robust to adjustment for confounders. Table 2 shows the unstandardised coefficients in imputed and complete cases of model 2a after adjustment (standardised coefficients and R^2 are reported in Table S2). The path from IL-6 at age 9 to psychosis-like symptoms at age 18 via internalising symptoms at

age 9 was significant even after adjustment (indirect effect: β=0.005; p<0.01; CI=0.00-0.00).

4. Discussion

To the best of our knowledge this is the first study showing a mediator effect of internalising, but not externalising, symptoms on the positive association between levels of IL-6 at age 9 and PLEs at age 18. The mediator effect persisted after adjusting for several potential confounders, including gender, ethnicity, BMI, social class, and maternal education and depression.

The finding of an association between inflammation and PLEs is not new and is in line with existing evidence (Khandaker et al., 2014, Khandaker et al., 2015, Al-Diwani et al., 2017). More recently, a meta-analysis also suggested that elevated IL-6 might represent a core component of the pathophysiology of psychosis (Pillinger et al., 2018). This cytokine can cross the blood-brain barrier (Wang and Miller 2017), induce microglial activation (Streit et al., 2000) and influence secondary brain changes in areas of relevance for the psychosis continuum, in line with evidence showing that inflammation has a key role in the modulation of neurodevelopment (Jiang et al., 2018).

The association between inflammation and internalising symptoms also confirms previous findings implicating inflammatory proteins in the neurobiology of internalising disorders in children (Slopen et al., 2013). However, most of the findings are from cross-sectional studies. Our study, using longitudinal data, shows an association of IL-6 in childhood (age 9 years) with the intercept, but not the slope, of the internalising symptoms trajectory from childhood to adolescence (ages 9-16 years). This suggests that inflammation and internalising symptoms in late childhood are concurrently associated but inflammation in late childhood is not related

to how internalising symptoms change from late childhood to late adolescence, a period characterized by hormonal changes known to influence brain development and inflammation (da Silva et al., 2017). Fluctuations in sex hormones could thus be considered as a possible explanation for this null finding.

Our main contribution to the literature is, as discussed, that the longitudinal association between inflammation in childhood and the onset of psychotic like experiences in adulthood is mediated by childhood internalising (but not externalising) psychopathology. Internalising symptoms are more tightly linked to the pathophysiology of the psychosis continuum than externalising symptoms are and high rates of internalising symptoms have been described in the prodromal phase of psychotic disorders (Fusar-Poli et al., 2012). Further, internalising symptoms, similar to inflammation, but unlike externalising symptoms, are associated with an increased risk of developing chronic physical comorbidities (van de Pavert et al., 2017), highly prevalent in psychosis sufferers (Hert et al., 2011). This suggests a shared pathophysiological background between inflammation, internalising symptoms and PLEs, which could explain our findings.

Our study has some important limitations that we must acknowledge. First, inflammation was only assessed once. Second, given the observational design, causality could not be inferred. Relatedly, there may be unobserved confounders including parental mental health problems or disorders other than antenatal maternal depression. Third, internalising and externalising symptoms in children were reported by mothers, which may raise concerns about potential reporter bias. However, we controlled for maternal depression and thus likely reduced reporter bias substantially.

Conclusion

Our findings suggest that low-grade inflammation during childhood may increase risk of psychotic-like experiences in early adulthood via increased childhood internalising symptoms. Both internalising symptoms (van de Pavert et al., 2017) and inflammation are associated with a greater risk of developing chronic physical disorders, which are often comorbid with psychosis (Hert et al., 2011) and thought to represent a phenotypic manifestation of a shared pathophysiological background (Minichino et al., 2017). These findings, obtained from a large, general population sample, provide an additional step towards understanding the relationship between inflammation and symptoms of the psychosis continuum.

Acknowledgments and Disclosures

We are extremely grateful to all the families who took part in this study, the midwives for their help in recruiting them, and the whole ALSPAC team, including interviewers, computer and laboratory technicians, clerical workers, research scientists, statisticians, volunteers, managers, receptionists and nurses. The UK Medical Research Council and Wellcome (Grant ref: 102215/2/13/2) and the University of Bristol provide core support for ALSPAC. A comprehensive list of grants funding is available on the ALSPAC website (http://www.bristol.ac.uk/alspac/external/documents/grant-acknowledgements.pdf). Dr Khandaker acknowledges funding support from the MQ: Transforming Mental Health (Data Science Award; grant code: MQDS17/40), the Wellcome Trust (Intermediate Clinical Fellowship; grant code: 201486/Z/16/Z), and the Medical Research Council (MICA: Mental Health Data Pathfinder; grant code: MC_PC_17213). This publication is the work carried out for a project funded by the UK Economic and Social Research Council (Grant ref: ES/P001742/1; PI Eirini Flouri). Prof Eirini Flouri and Dr Marta Francesconi will serve as

guarantors for the contents of this paper. The authors report no biomedical financial interests or potential conflicts of interest.

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